

A31869 A

(SHEET 1 OF 22)

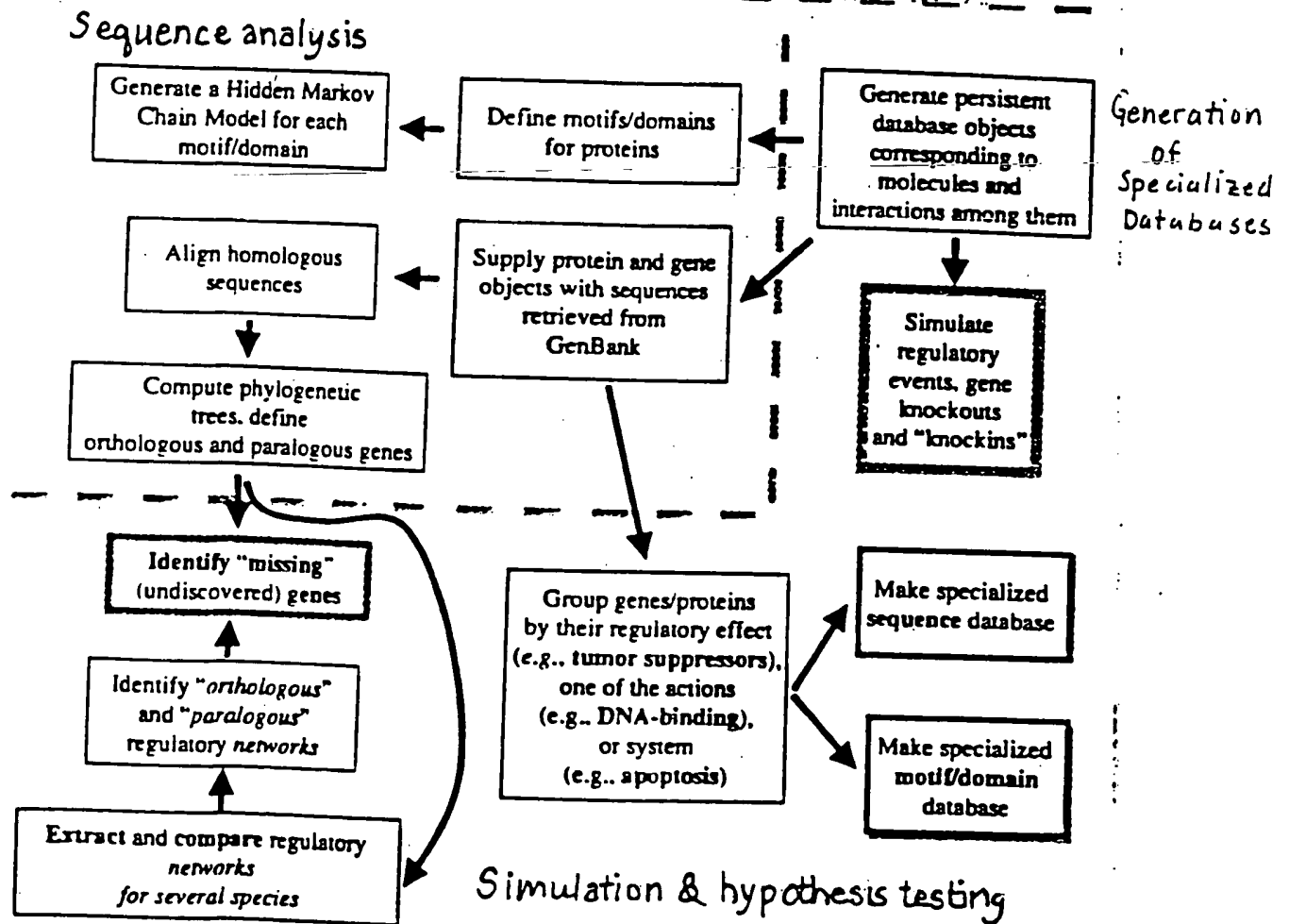


FIGURE 1

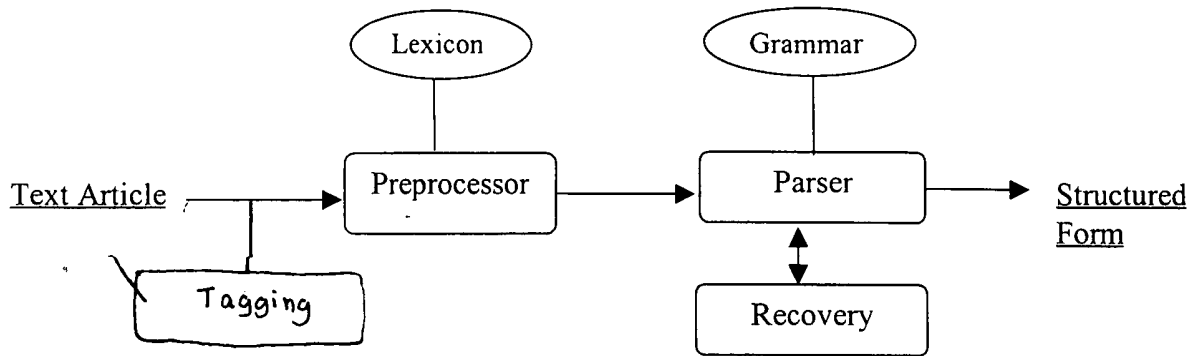


Figure 2

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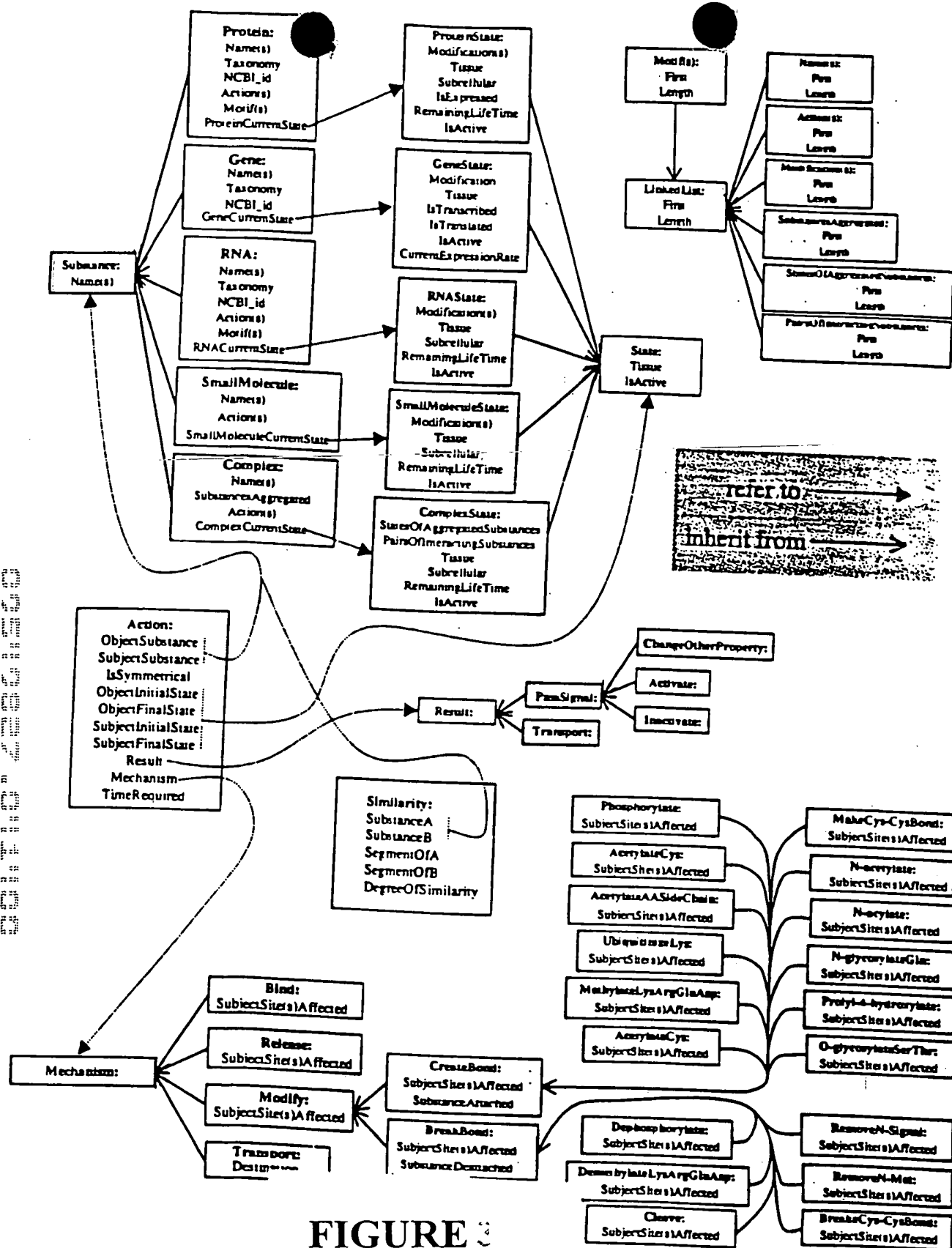


FIGURE 3

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FIGURE 4

bcl-2L / bcl / bcl-xS / ced-9 / Bax / Bkl / Bak / p21 / NGF1-B / N10 / Nak1 / Nur77 / Nurrl / Nor-1 / Not-1 / RXR / galectin-1 / N-glycan
/ CNTF / lck / fyn / ZAP-70 / raf / ras / MAP / protein kinase C / PKC / phosphatase calcineurin / NF-AT / AP1 / 14-3-3 / Raf-1 /
Bcl-2 / Interleukin / IL-1 / IL-3 / cytokine / IGF-1 / CD95 / Apo-1 / RIP / FAF1 / FADD / FAP-1 / TNFR / TRAF / TRAP1 /
TRAP2 / TRADD / H1AP1 / H1AP2 / CD40 / CD30 / XIAP / CD2 / CD3 / TCR / Bcl-w / Mcl-1 / NR-13 / BHRF1 / HMW5-HL /
E1B19K / Nbk / Mch2 / CPP32 / ICE / FLICE / Nedd-2 / TX / Mch3 / Mch4 / ICH-1a / nuc-1 / DNase1 / caspase / MACH1 /
Mch5 / apopain / Yama / ICH / CMH / ced-3 / ced-4 / ced-9 / p53 / MKK3 / MKK1 / MKK2 / MKK4 / BAG-1 / Src / FAST /
p38 / p42 / ERK1 / p44 / ERK2 / SAPK / JNK / MEK / C-JUN / MEF2D / ATF2 / calcineurin / ELK-1 / protein phosphatase 2A /
raf-1 / IL-1 beta / TNF / PTK / Apaf / p35 / ETS / C-Myc / IL-2 / IL-2 receptor / NF-kappa B / TNFR-1 / TRAIL / Apo-2L /
DR4 / death receptor / DR3 / DR2 / DR5 / DR1 / bad / BMPR / BMP-x / TGF / grim / hid / FAN / perforin / Fas-L / Fas / DcR1
/ decoy receptor / wsl-1 / NGF receptor / growth factor / RAR

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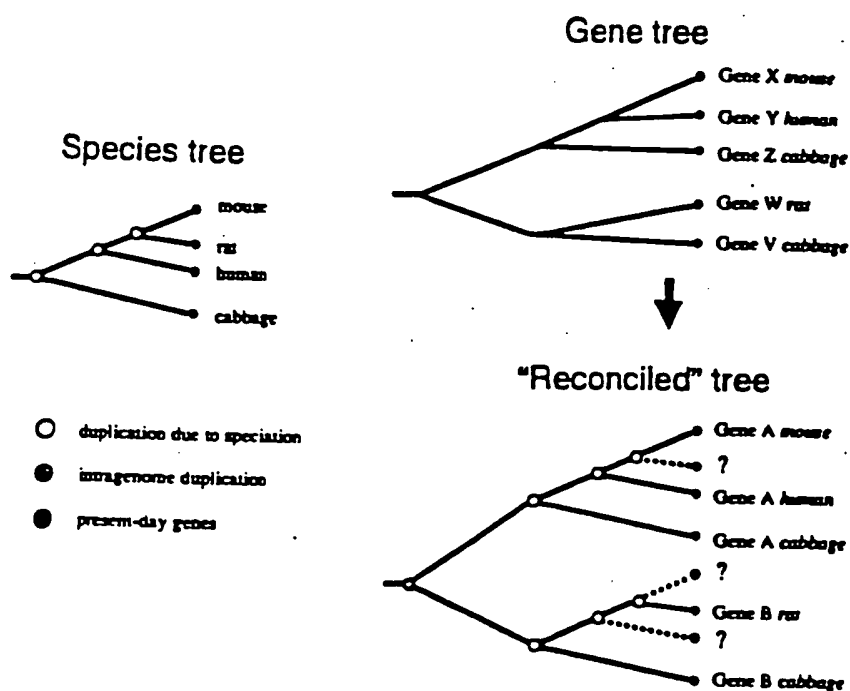


FIGURE 5

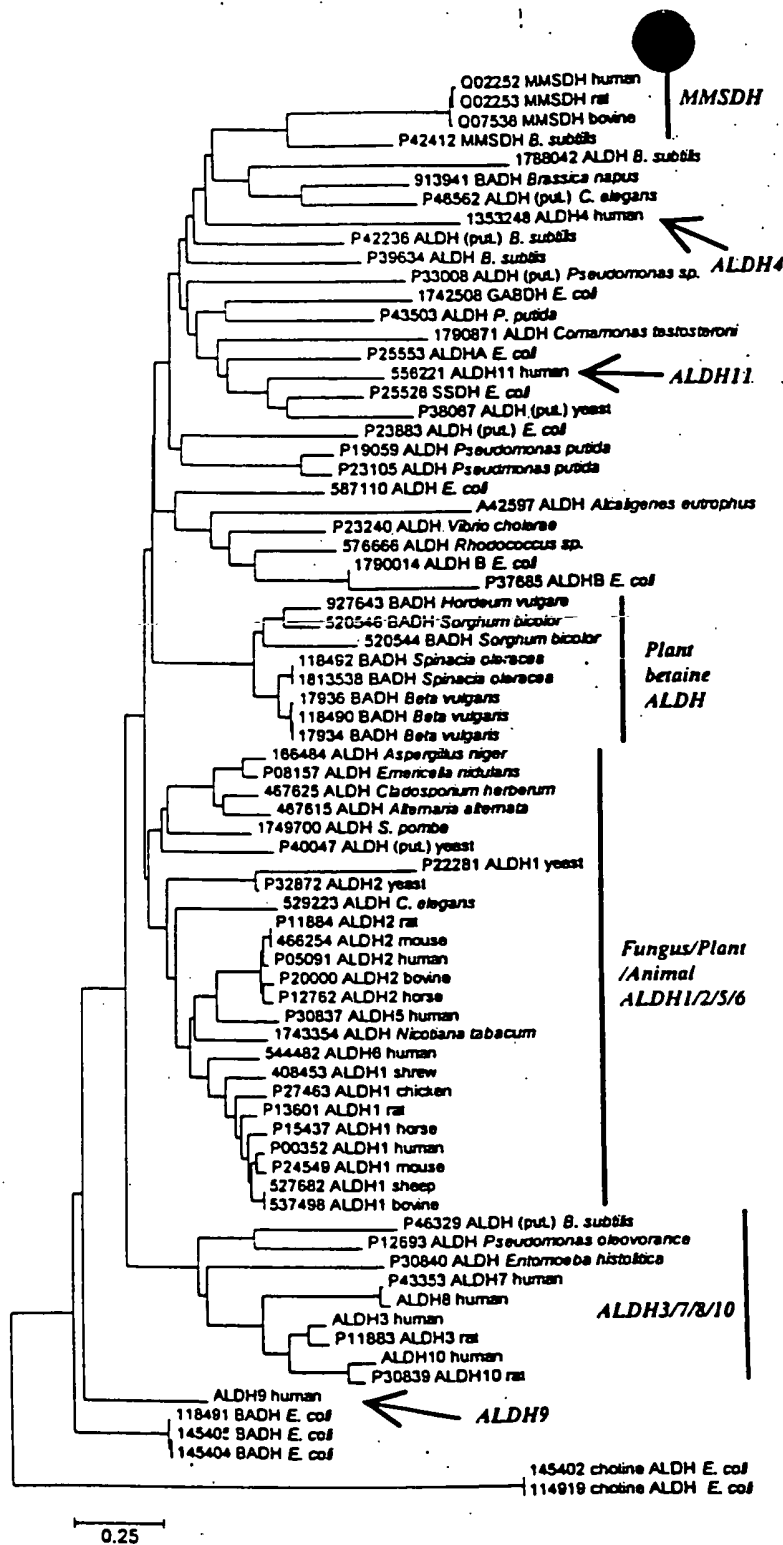


FIGURE 6

A31869A

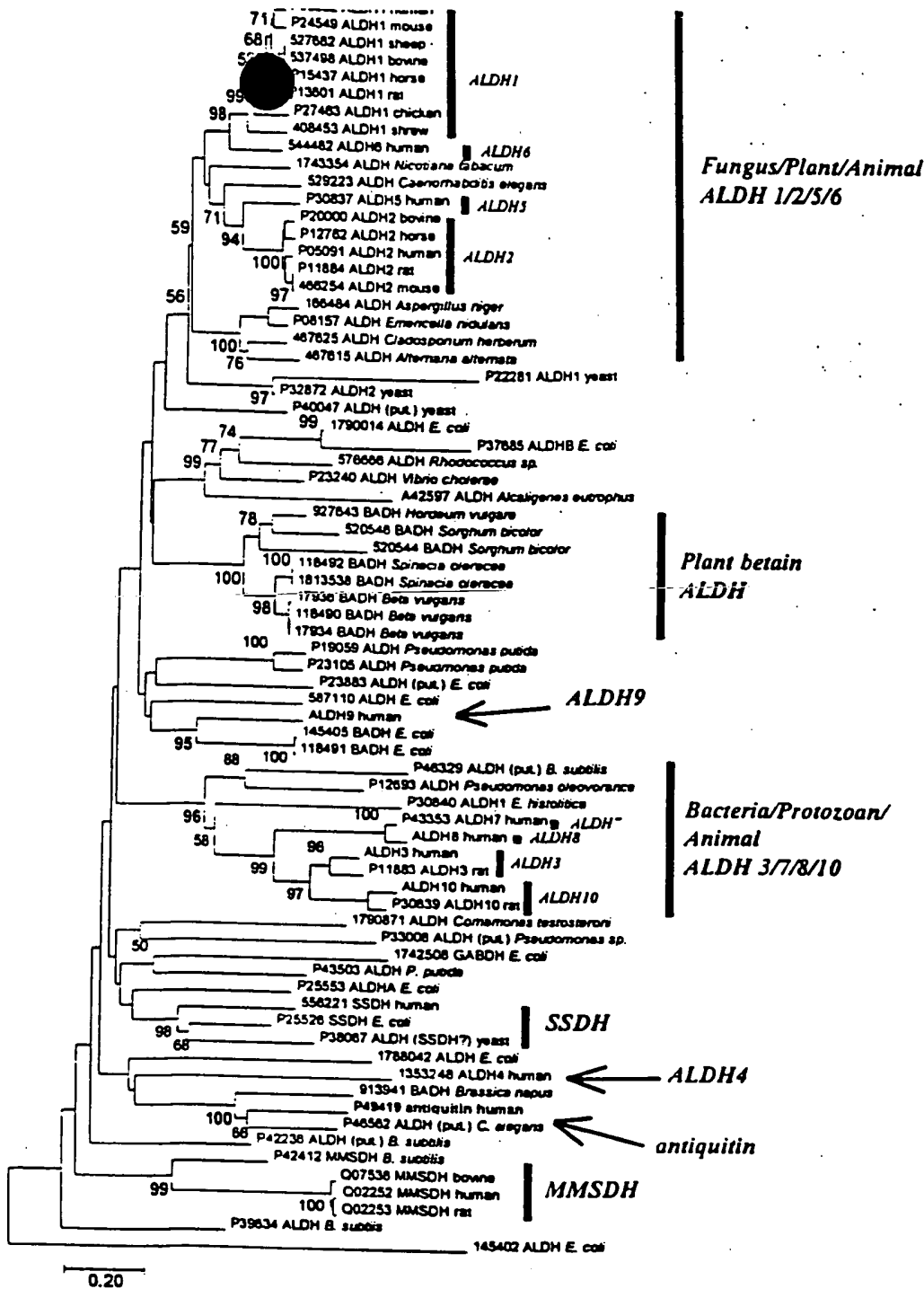


FIGURE 7

A31869 A

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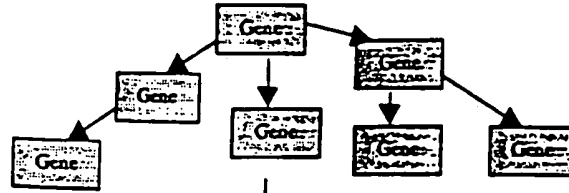
FIGURE 8

Start with a single Biological system

Start with a single gene

Start with a gene family

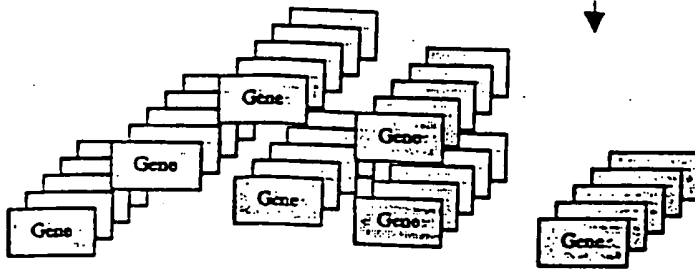
Reconstruct a "network" of interacting genes and proteins



Identify a set of key domains and motifs

Search for related motifs in databases of known organisms

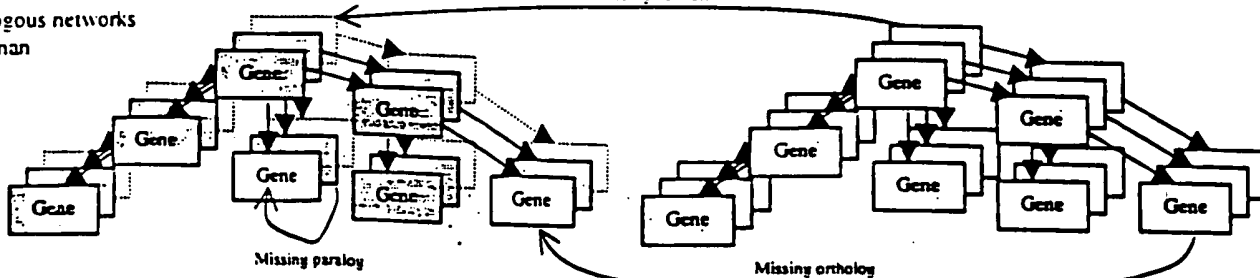
Identify members of multigene families



Compute phylogenetic trees

Identify clusters of paralogous genes. identify paralogous and orthologous networks

Paralogous networks in human



Compare regulatory schemes. identify genes that are known in one but missing in another system.
Find the genes using experimental techniques.

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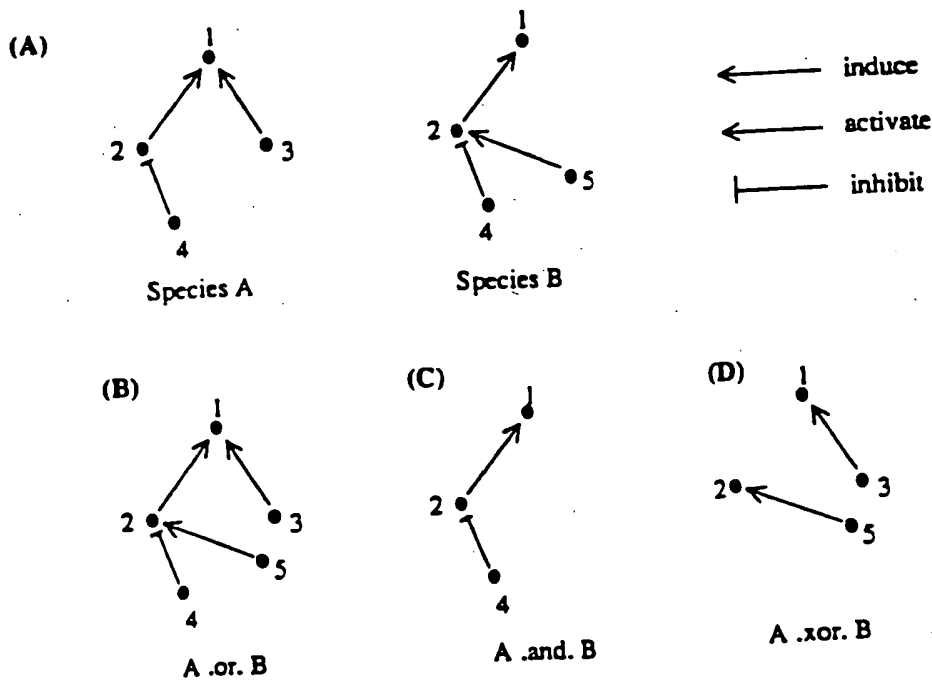


FIGURE 9

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(SHEET 10 OF 23)

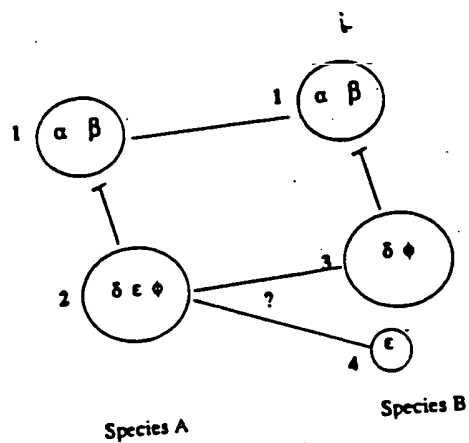


FIGURE 10

A31869 A

(SHEET 11 OF 23)

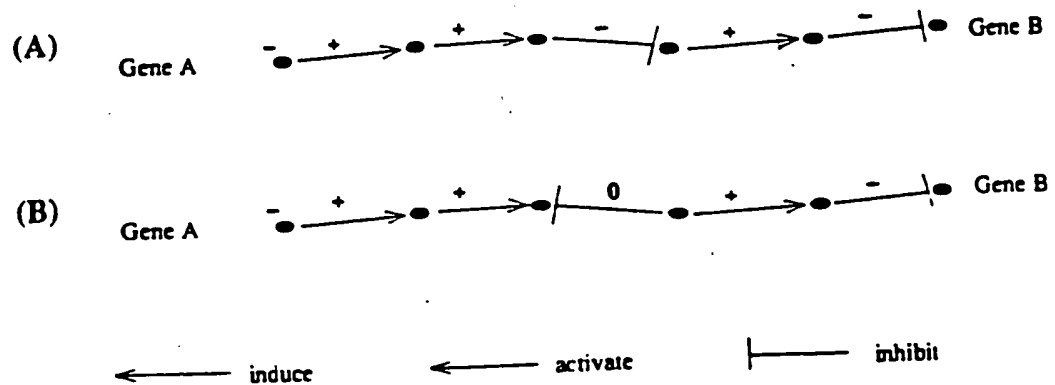


FIGURE 11

(SHEET 12 OF 23)

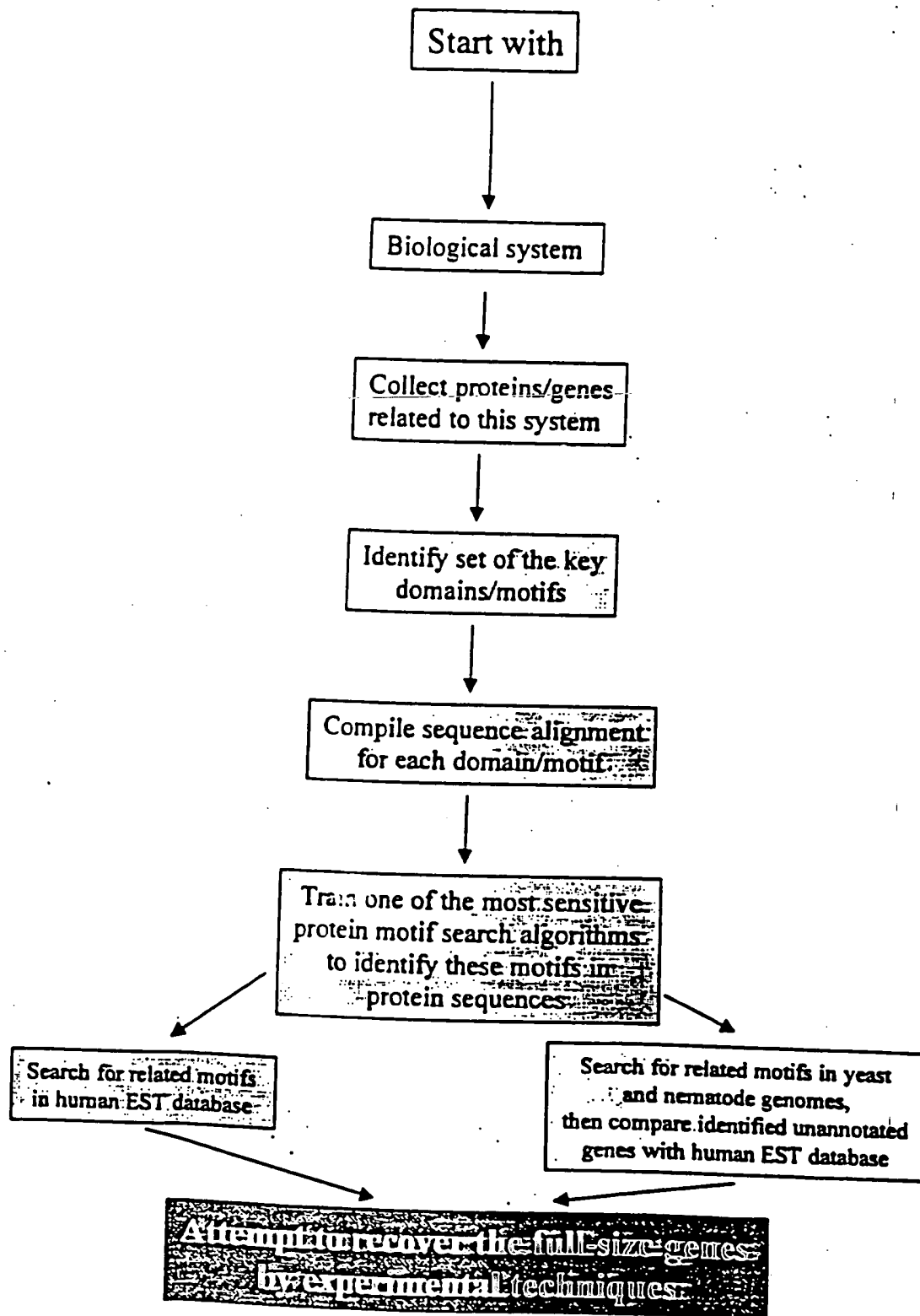


FIGURE 12

A31869A (sheet 13 of 23)

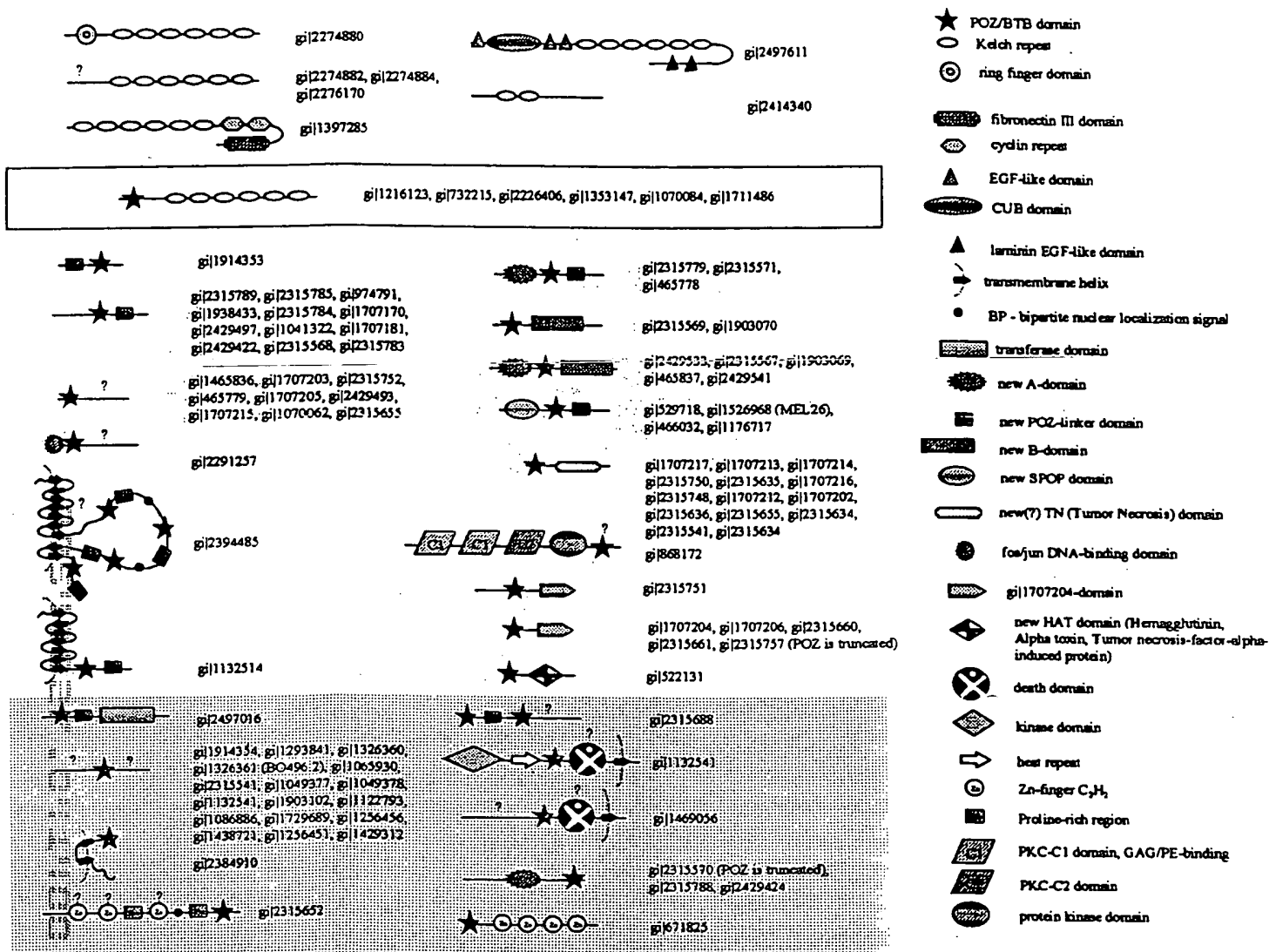


Figure 13.

A31869A
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>gi|2210766|gb|AA481214|AA481214 aa34e02.r1 NCI_CGAP_GCB1 Homo sapiens cDNA clone
IMAGE:815162 5' similar to WP:W07A12.4 CE03795 ;, mRNA sequence [Homo sapiens]
CATGGCTTCCTGGACACCAACCCTGCCATCCGGGAGCAGACGGTCAAGTCCATGCTGCTCCTGGCCCCAA
AGCTGAACGAGGGCCAACCTCAATGTGGAGGTGATGAAGCACTTTGCACGGCTACAGGCCAAGGATGAACA
GGGCCCCATCCGCTGCAACACCACAGTCTGCCTGGGCAAAATCGGCTCCTACCTCAGTGCTAGCACCAGA
CACAGGGTCCTTACCTCTGCCTTCAGCCGAGCCACTAGGGACCCGTTTGACCCGTCCCGGGTTGCGGGTG
TCCTGGGCTTTGCTGCCACCCACAACCTCTACTCAATGAACGACTGTGCCAGAAAGATCCTGCCTGTGCT
CTGCGGTCTCACTGTAGATCCTGAGAAATCCGTGCGAGACCAGGCCTTCAAGGCA

>gi|1349211|gb|W51957|W51957 zc45f01.r1 Soares_senescent_fibroblasts_NbHSF Homo
sapiens cDNA clone IMAGE:325273 5', mRNA sequence [Homo sapiens]
CCTTCGAGTTCGGCAATGCTGGGGCCGTTGCTCAGCCCCCTCTTCAAGGTGGGCAAGTTCCTGAGCGC
TGAGGAGTATCAGCAGAAGATCATCCCTGTGGTGGTCAAGATGTTCTCATCCACTGACCGGGCCATGCGC
ATCCGNCTCCTGCAGCAGATGGAGCAGTTTACCTGACGAGCCAACAGTCAACACCCAGATCT
TCCCCACGTCGTACATGGCTTCTGGACACCAACCCTGCCATCCGGGAGCAGACGGTCAAGTCCATGCT
GCTCCTGGCCCCAAAGCTGAACGAGGCCAACCTCAATGTGGAGCTGATGAAGCACTTTGCACGGCTACAG
GCCAAGGATGAACAGGGCCCCATCCGCTGCAACACCACAGTCTGCCTGGGCAAAATCGGCTCCTACCTCA
GTGCTAGCACCAGACACAGGGTCCTTACCTCTG

Figure 14A

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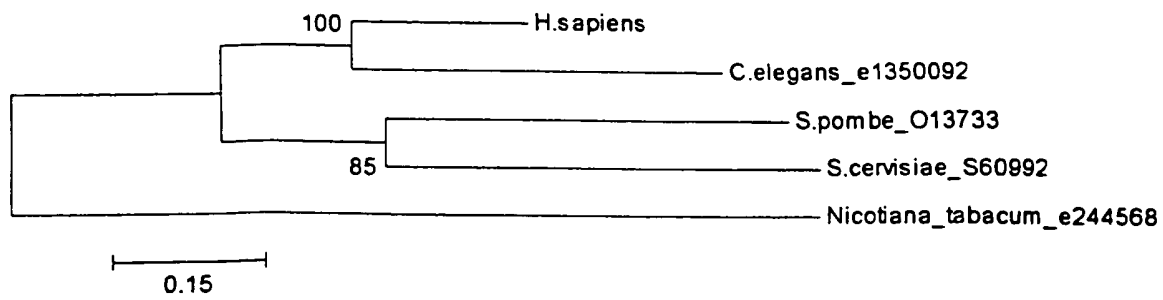


Figure 14B

A 31869A

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BASE COUNT	405 a	545 c	493 g	278 t	6 others	
ORIGIN						
1	cagccgaagc	amgcaaaaat	tcttccagga	gctgagcaag	agcctggacg	cattccctga
61	ggayttctgt	cggcacaagg	tgctgcccc	gctgctgacc	gccttcgagt	tccggcaatgc
121	tggggccggt	gtcctcacgc	ccctcttcaa	ggtgggcaag	tccctgagcg	ctgaggagta
181	tcagcagaag	atcatccctg	tggtgggtcaa	gatgtttctca	tccactgacc	gggccaatgcg
241	catccgcctc	ctgcagcaga	tggagcagtt	catccagtag	cttgacgagc	caacagtcaa
301	cacccagatc	ttccccacg	tcgtacatgg	cttctctggac	accaaccctg	ccatccggga
361	gcagacggtc	aagtccatgc	tgctcctggc	cccaaagctg	aacgaggcca	acctcaatgt
421	ggagctgatg	aagcactttg	cacggctaca	ggccaaggat	gaacagggcc	ccatccgctg
481	caacaccaca	gtctgocctg	gcaaaaatcgg	ctcctacctc	agtgtagca	ccagacacag
541	ggtccttacc	tctgccttca	gccgagccac	tagggaccg	tttgacacgt	cccgggttgc
601	gggtgtcctg	ggctttgtctg	ccaccacaaa	cctctactca	atgaacgact	gtgcccagaa
661	gatcctgcct	gtgctctgcg	gtctcactgt	agatcctgag	aaatccgtgc	gagaccaggc
721	cttcaaggcm	wttcggagct	tectgtccaa	attggagtct	gtgtcggagg	acccgaccca
781	gctggaggaa	gtggagaagg	atgtccatgc	agcctccagc	cctggcatgg	gaggagccgc
841	agctagctgg	gcaggctggg	cgtgaccggg	gtctcctcac	tcacctccaa	gctgatccgt
901	tcgcacccaa	ccactgcccc	aacagaaacc	aacattcccc	aaagacccac	gcctgaagga
961	gttcctgccc	cagccccccac	ccctgttcc	gccaccccta	caacctcagg	ccactgggag
1021	acgcaggagg	aggacaagga	cacagcagag	gacagcagca	ctgctgacag	atgggacgac
1081	gaagactggg	gcagcctgga	gcaggaggcc	gagtcctgtc	tggcccagca	ggacgactgg
1141	agcaccgggg	gccaaagtga	ccgtgctagt	caggtcagca	actccgacca	caaatectcc
1201	aaatccccag	agtccgactg	gagcagctgg	gaartcagg	gctcctggga	acagggctgg
1261	caggagccaa	gtctccagga	gccacctyct	gacggtacac	ggctggccag	cgagtataac
1321	tgggggtggc	cagagtccag	cgacaagggc	gaccccttcg	ctaccctgtc	tgcacgtccc
1381	agcaccagc	cgaggccaga	ctcttgggg	gaggacaact	gggagggcct	cgagactgac
1441	agtcgacagg	tcaaggctga	gctggcccgg	aagaagcgcg	aggagcgggc	gcgggagatg
1501	gaggccaaac	gcgcccagag	gaagggtgca	agggccccat	gaagctggga	gcccgggaagc
1561	tggactgaac	cgtggcggtg	gcccttcccg	gctgcccaga	gcccggccca	cagatgtatt
1621	tattgtacaa	accatgtgag	cccggccggc	cagccaggcc	atctcacgtg	tacataatca
1681	gagccacaat	aaattctatt	tcacaaaaaa	aaaaaaaaaa	aaaaaaa	

Figure 14C

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	5	10	15	20	25	30																								
1	S	R	S	X	Q	K	F	F	Q	E	L	S	K	S	L	D	A	F	P	E	D	F	C	R	H	K	V	L	P	Q
31	L	L	T	A	F	E	F	G	N	A	G	A	V	V	L	T	P	L	F	K	V	G	K	F	L	S	A	E	E	Y
61	Q	Q	K	I	I	P	V	V	V	K	M	F	S	S	T	D	R	A	M	R	I	R	L	L	Q	Q	M	E	Q	F
91	I	Q	Y	L	D	E	P	T	V	N	T	Q	I	F	P	H	V	V	H	G	F	L	D	T	N	P	A	I	R	E
121	Q	T	V	K	S	M	L	L	L	A	P	K	L	N	E	A	N	L	N	V	E	L	M	K	H	F	A	R	L	Q
151	A	K	D	E	Q	G	P	I	R	C	N	T	T	V	C	L	G	K	I	G	S	Y	L	S	A	S	T	R	H	R
181	V	L	T	S	A	F	S	R	A	T	R	D	P	F	A	P	S	R	V	A	G	V	L	G	F	A	A	T	H	N
211	L	Y	S	M	N	D	C	A	Q	K	I	L	P	V	L	C	G	L	T	V	D	P	E	K	S	V	R	D	Q	A
241	F	K	A	X	R	S	F	L	S	K	L	E	S	V	S	E	D	P	T	Q	L	E	E	V	E	K	D	V	H	A
271	A	S	S	P	G	M	G	G	A	A	A	S	W	A	G	W	A													

Figure 14 D

>sp|P15533|RPT1_MOUSE DOWN REGULATORY PROTEIN
OF INTERLEUKIN 2 RECEPTOR (J03776) rpt-1r [Mus
musculus] Length = 353

Score = 92.0 bits (237), Expect = 6e-20

```
Query 194 VMELLEEDLTCPICCSLFDDPRVLPCSHNFCKKCLEGILEGSRNSMWRPAPFKCPTCRK 373
          V+E+++E++TCPIC L +P C+H+FC+ C+ E S RN+ CP CR
Sbjct 5 VLEMIKEEVTCPICLELLKEFVSADCNHSFCRACITLNYE-SNRNT---DGKGNCPVCRV 60

Query 374 ETSATGINSLQVNYSLKGIVEKYNKIKISP-----KMPVCKGHMGQPLNIFCLTDMQLICG 541
          +L+ N + IVE+ K P K+ +C H G+ L +FC DM +IC
Sbjct 61 PYP---FGNLRPNLHVANIVERLKGFKSIPEEEQKVNICAQH-GEKLRLFCRKDMMVICW 116

Query 542 ICATRGENTKGVFCSIEDAYAQERDAFESLFQSF-----ETWRRGDALSRLDTMETSK 700
          +C EH H IE+ + ++ + + W+ L R+D
Sbjct 117 LCERSQEHGRGHTALIEEVDQYKEKLOGALWKLKKAQICDEWQDDLQLQRVDW----- 171

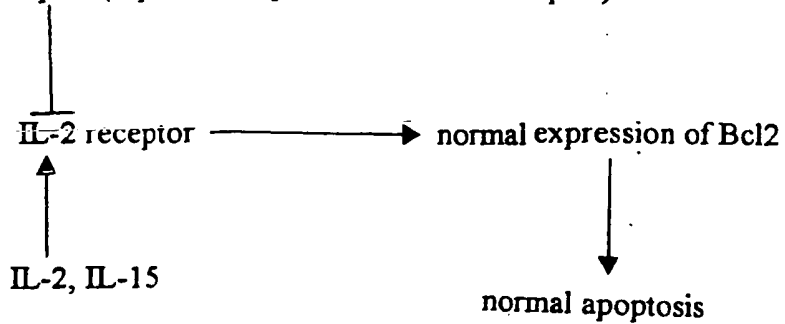
Query 701 RKSLQLMTKDSKVKKEFFEKLQHTLDQKKNEILSDFETMKLAVMQAYDPEINKL 862
          +Q+ + + V+ F+ L+ LD K+NE L + K VM+ + N+L
Sbjct 172 ENQIQI---NVENVQRFKGLRDLLDSKENEELQKLKKEKKEVMEKLEESENEL 222
```

Homology covers ring finger, B-box and the beginning of coiled coil domain
in the CLL ring finger protein

Figure 15

Activated CD4⁺ T-cells

Rpt1 (represses expression of IL-2 receptor)



When rpt1 is knocked out:

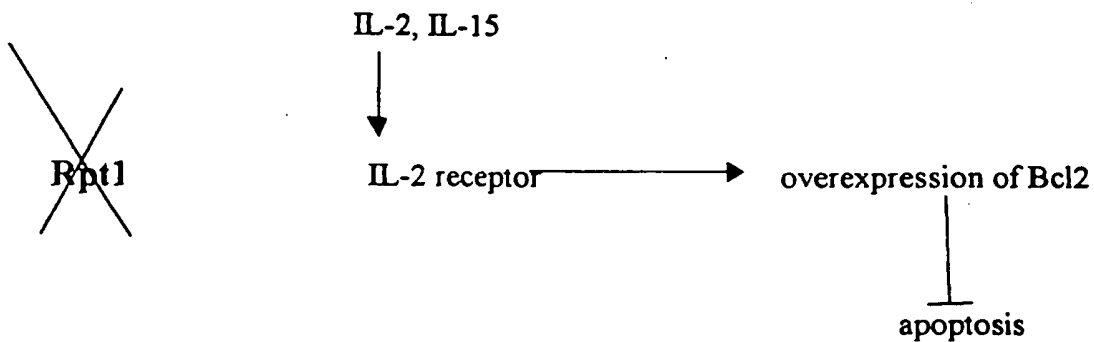


Figure 16

TBLASTN 2.0.8 [Jan-05-1999]

Reference:

Altschul, Stephen F., Thomas L. Madden, Alejandro A. Schäffer, Jinghui Zhang, Zheng Zhang, Webb Miller, and David J. Lipman (1997), "Gapped BLAST and PSI-BLAST: a new generation of protein database search programs", Nucleic Acids Res. 25:3389-3402.

Query= gi|21374984|Med3m
(205 letters)

gb|AA278224|AA278224 zs77e05.r1 NCI CGAP GCB1 Homo sapiens cDNA clone IMAGE:703520 5'
similar to TR:G1184157 G1184157 MAX-INTERACTING
TRANSCRIPTIONAL REPRESSOR. ;
Length = 430

Score = 209 bits (526), Expect = 1e-53
Identities = 104/124 (83%), Positives = 116/124 (92%), Gaps = 1/124 (0%)
Frame = +2

Query: 1 MEPVASNIQVLLQAAEFLERREREAHGYASLCPHHSPGTVCCRRKPPLQAPGALNSGRS 60
MEP+ASNIQVLLQAAEFLERREREAHGYASLCPH SPG + RR+K P QAPGA +SGRS
Sbjct: 56 MEPLASNIQVLLQAAEFLERREREAHGYASLCPHSPGPIHRRKKRPPQAPGAQDSGRS 235
Query: 61 VHNELEKRRRAQLKRCLEQLRQOMPLGVDCTRYTTLSSL-RARVHIQKLEEQEQARRLK 119
VHNELEKRRRAQLKRCLE+L+QOMPLG DC RYTTLSSL RAR+HIQKLE+QEQ+AR+LK
Sbjct: 236 VHNELEKRRRAQLKRCLEQLRQOMPLGGDCARYTTLSSLRRARMHIQKLEDQEQRRARQLK 415
Query: 120 EKLRS 124
E+LR+
Sbjct: 416 ERLRT 430

dbj|C02407|C02407 HUMGS0012279, Human Gene Signature, 3'-directed cDNA sequence.
Length = 348

Score = 97.5 bits (239), Expect = 6e-20
Identities = 51/63 (80%), Positives = 56/63 (87%)
Frame = +3

Query: 125 KQOSLQQLEQLQGLPGARERERLRADSLDSSGLSSERSDSQEDLEVDVENLVFGTETE 184
KQOSLQ+ QL+GL GA ERERLRADSLDSSGLSSERSDSQEQ+LEV DVE+LVFG E E
Sbjct: 45 KQOSLQRXWMLRGLAGAAERERLRADSLDSSGLSSERSDSQEELEV DVESLVFGGEAE 224
Query: 185 LLQ 187
LL+
Sbjct: 225 LLR 233

Figure 17 A

BASE COUNT	130 a	234 c	258 g	106 t	5 others	
ORIGIN						
1	cagccgcttg	ctccggccgg	caccctaggc	cgcagtcgcg	caggctgtcg	ccgacatgga
61	acccttggcc	agcaacatcc	aggtcctgct	gcaggcggcc	gagttcctgg	agcgccgtga
121	gagagaggcc	gagcatgggt	atgcgtccct	gtgcccgcat	cgcagtcag	gccccatcca
181	caggagggaag	aagcgacccc	cccaggtccc	tggcgcgag	gacagcgggc	ggtcagtga
241	caatgaactg	gagaagcgca	ggagggccca	gttgaagcgg	tgcctggagc	ggctgaagca
301	gcagatgccc	ctgggcggcg	actgtgcccg	gtacaccacg	ctgagcctgc	tgcgccgtgc
361	caggatgcac	atccagaagc	tggaggatca	ggagcagcgg	gcccgcagc	tcaaggagag
421	gctgcgcaca	aagcagcaga	gcctgcagcg	gcantggatg	cagctccggg	ggctggcagg
481	ngcggccgag	cgggagcgnc	tgcgggcgga	cagtctggac	tcctcaggcc	tctcctctga
541	gcgctcagac	tcagaccaag	aggagctgga	ggtggatgtg	gagagcctgg	tgtttggggg
601	tgaggccgag	ctgctgcggg	gcttcgtcgc	cggccaggag	cacagctact	cgcacgtcgg
661	cggcgctg	ctatgatgtt	cctcacccan	ggcgggcctc	tgccctctta	ctcgttgccc
721	aagcccactt	tnc				

Figure 17B

C

>Mad3h(Putative)

MEPLASNIQVLLQAAEFLERREREAEHGYASLCPHRSPGPIHRRKKRPPQAPGAQDSGRSVHNELEKRRRAQLK
RCLERLKQOMPFGGDCARYTTLSLLRRARMHIQKLEDQEQRARQLKERLRTKQOSLQRXWMQLRGLAGAAERER
LRADSLDSSGLSSERSSDOELEVDVESLVFGGEAELLRGFVAGOEHSSYSHVGGAWL

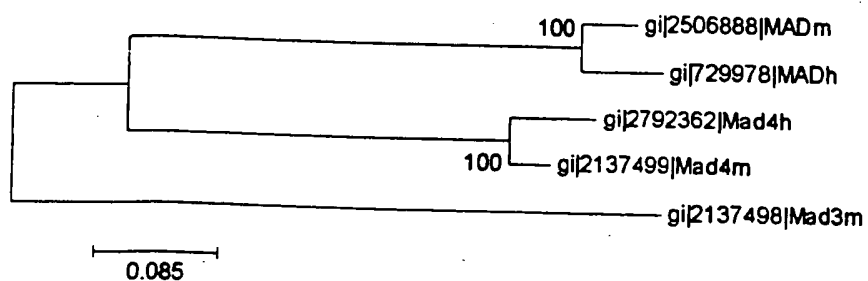
D

gi12506888 Madm	KATAVGHNIQLLLEAADYLERREAEHGYASMLPYS-KCRDAFKRRNKPKGNST--SSRSTHNEMEKNRAHLRLCLEKLGVLVLPPESSRHTTSL
gi1729978 Madh	HAAAVRNINQMLLEAADYLERREAEHGYASMLPYNKCDADALKRRNKSKGNNS--SSRSTHNEMEKNRAHLRLCLEKLGVLVLPPESSRHTTSL
gi12792362 Mad4h	---MELNSLLILLEAAEYLERRDREAEGYASVLPFDGDFAREKTKAAGLVKAP--NNRSSHNELEKHRAKLRLYLEQLKQLVLPDPSTRTHTTSL
gi12137499 Mad4m	---MELNSLLILLEAAEYLERRDREAEGYASVLPFDGDFARQKTKTAGLVKAP--NNRSSHNELEKHRAKLRLYLEQLKQLVLPDPSTRTHTTSL
gi12137498 Mad3m	-MEPVASNIQVLLQAAEFLERREREAEHGYASLCPHSPGTVCRRRKPPLOAPGALNSGRSVHNELEKRRRAQLKRCLEQLRQOMPFGVDCARYTTLS
Mad3h Putative	-MEPLASNIQVLLQAAEFLERREREAEHGYASLCPHRSPGPIHRRKKRPPQAPGAQDSGRSVHNELEKRRRAQLKRCLEQLRQOMPFGGDCARYTTLS
gi12506888 Madm	TKAKLHIKKLEDCORCAVHQIDQLOREQRHLKRRLEKLGAEIR-----MDSVG-SVVSERSSDSDRELDVDVDVDVDVVEGTDYLNGLGWSSS-
gi1729978 Madh	TKAKLHIKKLEDCORCAVHQIDQLOREQRHLKRRLEKLGAEIR-----MDSIG-STVVSERSSDSDRE-----EIDVDVESTDYLTGDLWSSSS-
gi12792362 Mad4h	KRAK/HIKKLEEQRRALSIKEQLQOEHRFLKRRLEQLSVQSVR-----VRTDSTG-SAVSTD--DSEOE-----VDIEGHEFGPGELDSVGS-
gi12137499 Mad4m	K-AQMHIKKLEEQRRALSIKEQLQOEHRFLKRRLEQLSVQSVR-----VRTDSTG-SAVSTD--DSEOE-----VDIEGHEFGPGELDSVGS-
gi12137498 Mad3m	R-ARVHIKKLEEQRRALSKEKLSKQOSLQOOLEQLQGLPGARERRLRADS LDSSGLSSERSSDSQE-----DLEVDVENLVFG-TETELLQSF
Mad3h Putative	RRARMHIKKLEQEQRARQLKERLRTKQOSLQRXWMQLRGLAGAAERERLRADSLDSSGLSSERSSDSQE-----ELEVDVESLVFG-GBAELLRGF
gi12506888 Madm	VSDSDERGSMQSLG-SDEGYSSATVKRAKLQDGHKAGLG-
gi1729978 Madh	VSDSDERGSMQSLG-SDEGYSSATVKRAKLQDGHKAGLG-
gi12792362 Mad4h	SSDADDHYSLQSGTGSGFGPHCRALGRFALS-----
gi12137499 Mad4m	SSDADDHYSLQSGTGSGFGPHCRALGRFALS-----
gi12137498 Mad3m	SAGREHSYSHSTCAWL-----
Mad3h Putative	VAGQERSYSHVGGAWL-----

Figure 17 C-D

A31869A
(Sheet 23 of 23)

A.



B.

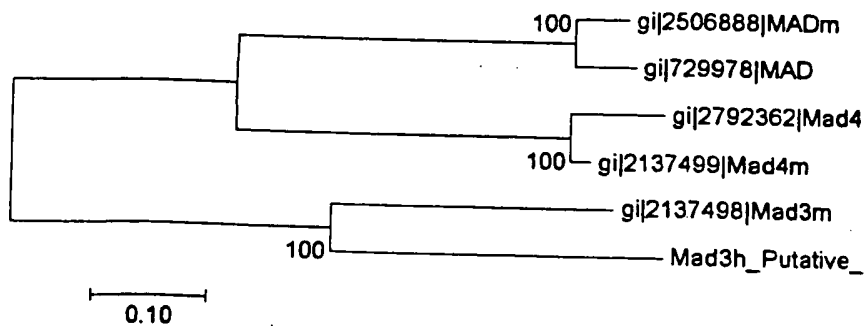


Figure 18. A-B